High Throughput Screening of Toxicity Pathways Perturbed by Environmental Chemicals

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Abstract

Toxicology, a field largely unchanged over the past several decades, is undergoing a significant transformation driven by a number of forces – the increasing number of chemicals needing assessment, changing legal requirements, advances in biology and computer science, and concerns over the use of animals in research. Here we report on the first results of a large-scale experiment to screen environmental chemicals using a battery of *in vitro* assays. EPA's ToxCast program screened 309 pesticide active and industrial chemicals in concentration-response format using 467 biochemical and cell-based assays across 9 different technologies that probe a large number of biological pathways. Many environmental chemicals were active across a wide range of pathways and processes, in some cases in the nanomolar range. *In vitro* assays were able to identify and detect known toxicity mechanisms of actions as well as to identify other, not previously reported, biological processes activated by these chemicals. Based on the data generated, we present an initial predictive signature for rat liver proliferative lesions based on 12 *in vitro* assays, including ones that measure affects on PPAR (peroxisome proliferator activated receptor) signaling, a well-known carcinogenic mode of action in rodents. Continuation of ToxCast promises to identify additional assays and pathways predictive of toxicity and human disease from environmental exposures, and to help transform the field of toxicology.

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